REMARKS

Status of the claims

Claims 1-4, 6, 9-12, 14, and 23-27 are pending in the present application and are currently under consideration. No claim amendments or cancellations have been made and no new claims have been added by virtue of this response.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement is submitted herewith. Applicants would appreciate the Examiner initialing and returning the Form SB/08, indicating that the references therein have been considered and made of record in the application.

Claim rejection under 35 U.S.C. §103(a)

Claims 1-4, 6, 9-12, 14, and 23-27 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Beutner et al. (1998) *Journal of the American Academy of Dermatology* 38(2):230-39 ("Beutner"), Bauman et al. (1996) *Pediatric Otolaryngology* 43(6):1385-1401 ("Bauman"), and Yamamoto et al. (1994) *Japanese Journal of Cancer Research* 85, 775-79 ("Yamamoto"), and further in view of Raz et al. (U.S. Patent No. 6,514,948) ("Raz") and Schwartz et al. (WO 98/55495) ("Schwartz"). Applicants respectfully traverse this rejection.

A. Response to assertions made by the Examiner in the Office Action

1. Response to assertions with respect to Bauman

Bauman teaches administration of interferon-α ("IFN-α") as a supplement to surgical removal of human papillomavirus ("HPV") lesions. The Examiner states that "the teachings of [Bauman] provide adequate grounds for a reasonable expectation of success that an adjuvant that induces IFN-α would be effective against HPV in view of the teachings of [Bauman] stating that 'Single and multi-institutional studies have subsequently confirmed that α-IFN decreases the

growth of papillomata or increases the time interval between surgical therapies.' . . . The teachings of [Bauman], indicating that IFN-α does delay or [inhibit] symptoms of infections (thereby permitting greater periods of time between surgical treatments) provide sufficient grounds for those in the art to have a reasonable expectation that the presence of IFN-α alone would be effective." Office Action, paragraph bridging bottom of page 4 and top of page 5.

In response, Applicants respectfully note that the methods taught by Bauman differ from the presently claimed methods. Bauman teaches administration of IFN-α (rather than an ISS as claimed) subcutaneously, *i.e.*, systemically, rather than at the site of exposure to or at the site of a lesion of papillomavirus, *i.e.*, locally, as claimed. One of skill in the art would not expect success when switching from one mode of administration to another. Different formulation parameters, such as carrier(s) and additive(s) would have to be developed and tested empirically with respect to effectiveness for local administration and for effectiveness of the active agent against papillomavirus when administered locally. In fact, because Bauman teaches adjuvant therapies to surgical excision, administration of any therapeutic substance as a supplement to surgical therapy would necessarily be at a site *other than a lesion* (as such lesion would have been removed), and therefore Bauman teaches away from the claimed invention.

Further, direct administration of IFN-α, as taught in Bauman, would not provide a reasonable expectation of success when administering a different, structurally unrelated substance (an ISS-containing polynucleotide) which allegedly induces IFN-α production indirectly. There is no teaching in any of the cited references of the amount of IFN-α produced by administration of an ISS, so one of skill in the art would not know from these references if the amount of IFN-α produced would be equivalent to the dosages taught in Bauman (1 – 3 MU/m^2 body surface). A skilled artisan would not know how to correlate these dosages with the amount of IFN-α that might be induced, if at all, by administration of an ISS. Further, neither Raz nor Schwartz demonstrates induction of IFN-α. Both of these references mention detection of "an increase in levels of IL-12, IL-18 and/or IFN (α, β, or γ)" as a means of assessing stimulation of a Th1-type immune response. Raz , column 5, lines 8-11; Schwartz, page 9, lines 3-10. However, neither of these references exemplifies induction of IFN-α with an ISS, so it would not be possible for a person of skill in the

art to ascertain how much ISS would need to be administered to achieve the same dosage of IFN-α as the effective dosage taught by Bauman.

2. Response to assertions with respect to Beutner

Beutner teaches administration of imiquimod, for treatment of genital warts. Imiquimod is a non-nucleoside heterocyclic amine that is structurally unrelated to the claimed ISS-containing polynucleotides. In response to Applicants' previous arguments that cytokine inducers, such as imiquimod as taught in Beutner, are unpredictable in terms of treatment of viral infections, the Examiner states the references provided by Applicants in this regard are "not persuasive in view of the teachings of [Bauman] relating specifically to papillomaviral infections" Applicants respectfully note that *Bauman does not teach use of a cytokine inducer* to treat HPV. Rather, *Bauman teaches direct administration of a cytokine*, IFN-α. Thus, the teachings of Bauman do not address the known unpredictability in art with respect to treatment of viral infections with cytokine inducers.

Further, Applicants have previously noted that imiquimod is disclosed as inducing IFN-α as well as "a variety of cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)." Beutner, page 231. Beutner also states that "[i]n human peripheral blood mononuclear cells, imiquimod induces IFN-α, IL-1, and TNF-α, but not IL-2. Human keratinocytes exposed to imiquimod demonstrate an increase in messenger RNA for IL-1, IL-6, and IL-8. *Which of these cytokines accounts for the clinical response is not yet known.*" Beutner, page 237, emphasis added. A person of skill in the art would not have a reasonable expectation of success in substituting one substance capable of inducing cytokines for another cytokine inducer, when the cytokine that produces the effect of interest (wart clearance) is not known. Further, the degree of IFN-α induction and the actual amount of IFN-α required to treat papillomavirus are not disclosed in this reference. As discussed above, neither Raz nor Schwartz demonstrates IFN-α induction or discloses amount of IFN-α produced for a particular dosage of ISS. Therefore, it would not be possible for a person of skill in the art to correlate the results of Beutner with an appropriate dosage of ISS that could induce the same amount of IFN-α, and there would therefore be no reasonable expectation of success in substituting an ISS-containing polynucleotide for imiquimod.

3. Response to assertions with respect to Yamamoto

In the Office Action, the Examiner states that "the Applicant asserts that the Yamamoto reference fails to teach that ISS induce any cytokines." Office Action, page 4. Applicants disagree with the Examiner's characterization of their previous arguments with respect to Yamamoto. In the Supplemental Response filed on November 17, 2005, Applicants stated that "Yamamoto teaches that certain synthetic oligonucleotides stimulate production of a variety of cytokines, especially IFN-α, -β, and -γ. . . .Yamamoto does not disclose any viral treatment and shown only *in vitro* results in murine spleen cells. Accordingly, Yamamoto does not teach or suggest that ISS induces any cytokines *in vivo*, including IFN-α." 11/17/05 Response, page 8. Thus, Applicants argued that *Yamamoto does not teach induction of cytokines in vivo*, **not** that Yamamoto does not teach induction of any cytokines with an ISS.

Yamamoto teaches the ability of oligonucleotides to induce IFN-α, -β, and -γ in peripheral blood lymphocytes *in vitro*. Yamamoto discusses induced production of interferon in the context of antitumor activity, but *does not teach or suggest treatment of a viral infection*. All of the experiments in Yamamoto were performed *in vitro* in blood cells, and there is no teaching or suggestion of application to an *in vivo* viral infection as claimed.

The Examiner states that "[t]he additional teachings of Raz and Schwartz support [the] teachings [of Yamamoto] as previously described. The fact that Raz teaches a different method for administration is not found relevant or persuasive. . . The fact that Schwartz teaches that an oligonucleotide comprising the ISS and encoding an antigen is not found persuasive as the reference indicates that the IFN-inducing activity is due to the present of the ISS sequence." Office Action, paragraph bridging bottom of page 5 and top of page 6. Applicants respectfully disagree with the Examiner's reasoning. Yamamoto does not teach treatment of a viral infection *and* does not teach induction of IFN-α *in vivo*. Raz does not teach administration of an ISS at the site of exposure or at the site of a lesion of HPV as claimed. Raz teaches administration of an ISS prior to exposure to an antigen, versus the claimed methods that require administration after exposure. Schwartz does not teach administration of an ISS at the site of exposure or at the site of a lesion of HPV as claimed, much less in the absence of papillomavirus antigen as claimed. There would be no reasonable

expectation of success in treating an HPV infection *in vivo* extrapolating from Yamamoto's disclosed *in vitro* experiments and disclosure of antitumor activity. The teachings of Raz and Schwartz do not fill in the gaps from the teachings of Yamamoto to provide a reasonable expectation of success. There would also be no reasonable expectation of success in treating an HPV infection at the site of exposure or at the site of a lesion of HPV extrapolating from Raz's teaching of a different timing of ISS administration than Applicants' claimed method or in view of an absence of any teaching in Schwartz of administration of ISS at the claimed site of administration or in the absence of papillomavirus antigen as claimed.

B. The cited references do not support a prima facie case for obviousness

The Examiner's arguments in the Office Action all revolve around an alleged reasonable expectation of success in practicing the claimed methods in view of the cited references. However, a *prima facie* case of obviousness requires that *three* basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion of motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); MPEP §2143. All three elements of a *prima facie* case must be present in order for the Office to meet its burden. None of these three criteria for obviousness is satisfied by the currently cited references.

1. The cited references do not teach all of the elements of the claimed invention.

The present invention is directed to a method of delaying development of a lesion associated with papillomavirus infection or reducing severity of a lesion associated with papillomavirus infection, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS) comprising the sequence 5'-C,G,pyrimidine,

pyrimidine, C,G-3' at a site of exposure to papillomavirus (for methods of delaying development of a lesion) or at a papillomavirus-associated lesion (for methods of reducing severity of a lesion).

Neither Beutner, Bauman, nor Yamamoto teaches administration of a composition comprising an ISS-containing polynucleotide for delaying development or reducing severity of a papillomavirus lesion, much less at the site of exposure or at the site of the lesion, as claimed. The Examiner has admitted on the record that this combination of references does not teach the elements of the claimed invention. (See 12/16/04 Office Action, page 6, lines 1-3, withdrawing a previous rejection under 35 U.S.C. §103(a) over Beutner, Bauman, and Yamamoto. "The Applicant traverses this rejection in part because the references do not teach the use of the ISS sequences identified in the claims. This argument is found persuasive.")

Beutner teaches treatment of genital warts with imiquimod, a non-nucleoside cyclic amine, and *does not teach or suggest administration of an ISS*. Bauman teaches treatment of respiratory papillomatosis with surgical excision in conjunction with additional therapeutics as an adjunct to surgery, but *does not teach or suggest administration of an ISS*. Yamamoto teaches use of synthetic oligonucleotides for stimulation of interferon α, β, and γ production in murine spleen cells *in vitro* but *does not teach or suggest treatment of a viral infection*. Further, *none of these references teaches administration of an ISS-containing polynucleotide at a site of exposure to or at a site of a lesion of papillomavirus*, as claimed. Thus, none of these references, either singly or in combination, teaches all of the elements of the present claims, as noted by the Examiner in the 12/16/04 Office Action.

Neither Raz nor Schwartz cures the deficiencies of Beutner, Bauman, and Yamamoto. Raz teaches administration of an ISS *prior to exposure* to an antigenic substance or microbial pathogen. Thus, the timing of administration is completely different than the claimed methods which require administration of an ISS-containing polynucleotide *after exposure* to papillomavirus (*i.e.*, at a site of exposure (for methods of delaying development) or at the site of a lesion (for methods of reducing severity of a lesion)). Further, *Raz does not disclose treatment of papillomavirus*. Thus, the teaching of Raz is deficient with respect to the same claim elements as Beutner, Bauman, and Yamamoto. *None of these references teaches administration of an ISS to*

treat a papillomavirus infection or administration of an ISS at the site of exposure to papillomavirus or at the site of a papillomavirus lesion.

Schwartz teaches administration of ISS oligonucleotides either (i) as the only immunologically active substance for a general stimulation of the immune system, or (ii) in conjunction with one or more immunomodulatory molecules either in the form of a conjugate or as an admixture. Page 12, lines 6-35. Schwartz mentions in general terms that the methods taught therein may be used to treat or prevent viral infections such as papillomavirus (page 5, lines 29-31 and lines 35-37). However, the only specific disclosure with respect to papillomavirus is in the context of methods for modulating an immune response, involving using a papillomavirus as a source of peptide antigens for inclusion in compositions comprising an ISS and antigenic peptides. Page 13, line 26 – page 14, line 3; page 21, lines 13-29. Schwartz discusses *co-administration* of an ISS and a peptide antigen derived from a microorganism such as papillomavirus to modulate an immune response to the antigen. This method differs from the presently-claimed methods which recite "a papillomavirus antigen is not administered in conjunction with administration of [an ISS-containing composition]." *Schwartz does not teach administration of an ISS alone (without virus-derived antigenic peptide) to treat a papillomavirus infection. Further, Schwartz does not teach or suggest administration of an ISS at the site of exposure to papillomavirus or at the site of a papillomavirus lesion, as claimed.* Thus, Schwartz does not cure the deficiencies of the other cited references, which also do not teach these elements of the claimed invention.

None of the cited references, either singly or in combination, teaches all of the elements of the claimed invention, as required to support a *prima facie* case for obviousness.

2. There is no suggestion or motivation to combine or modify the cited references.

A *prima facie* case for obviousness requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a cited reference or combine reference teachings. *In re Vaeck*, MPEP §2143.

The references provide no motivation to combine the teachings therein to arrive at the claimed invention. Indeed, this would be impossible since the cited references do not teach all of the elements of the claimed invention, as discussed above.

Further, there is no suggestion or motivation in the cited references to modify the teachings therein to arrive at the current invention. Nothing in the cited references would have provided motivation to a skilled artisan to administer an ISS at the site of exposure or at the site of a lesion to delay development or reduce severity of a papillomavirus infection as claimed. The Examiner's premise is that the primary references teach treatment of papillomavirus infections by administration or induction of IFN-α, and that one of skill in the art would be motivated to substitute an ISS, which allegedly induces IFN-α. Applicants respectfully submit that this premise is flawed because the Bauman and Buetner references do not provide a motivation to modify the treatment regimens disclosed therein and the Yamamoto reference does not teach or provide motivation for treating a viral infection.

Bauman is primarily concerned with surgical excision of recurrent respiratory papillomatosis ("RRP") lesions. "The mainstay of treatment for persons with RRP is surgical ablation of active disease." Bauman, page 1390. Bauman discusses various adjuvant therapies that may be used in conjunction with and as a supplement to surgical intervention. One of the adjuvant therapies discussed by Bauman is subcutaneous administration of IFN-α. Bauman does not provide a motivation to modify the teachings therein by administering a composition that induces IFN-α rather administering IFN-α directly. Bauman teaches that *direct* administration of IFN-α is an effective supplement to surgical intervention and that the side effects of such administration "rarely require cessation of therapy" (page 1395), so there would be no motivation to substitute another compound that *indirectly* induces IFN-α along with many other substances with potential unknown associated side effects. Bauman does not suggest that an indirect induction of IFN-α would be desirable or advantageous with respect to the direct administration taught therein. Thus, Bauman provides no motivation to modify the teachings therein by substituting an ISS, as taught in Raz and Schwartz, for IFN-α.

Beutner is concerned with treatment of genital warts with imiquimod, an inducer of a variety of cytokines including IFN-α. Beutner explicitly states that the cytokine responsible for clinical response to imiquimod "is not yet known." Beutner, page 237. Beutner teaches that imiquimod provides effective treatment with side effects "predominantly reported as mild or moderate and rarely as severe and . . . of a relatively short duration," with "no serious systemic adverse reactions or clinical laboratory abnormalities reported." Beutner, page 235. Since Beutner teaches that imiquimod administration results in effective treatment of genital warts without serious side effects, this reference does not provide motivation to substitute another, structurally unrelated substance such as an ISS, as taught in Raz and Schwartz. With respect to the Examiner's premise that an ISS, which allegedly induces IFN-α, could be substituted for imiquimod, there would be no motivation to do so, in view of the statement in Beutner that the cytokine responsible for the observed treatment effect is unknown.

As discussed above, Yamamoto teaches the ability of oligonucleotides to induce cytokines, including IFN-α, *in vitro*, and discusses use of such induction for treatment of tumors. Yamamoto does not teach or suggest treatment of a viral infection. Yamamoto does not provide motivation to modify the teachings therein to arrive at the claimed invention, because this reference does not teach or suggest that induction of interferons could be applied to treatment of a viral infection.

Raz does not teach administration of an ISS at the site of exposure to papillomavirus or the site of a papillomavirus lesion and does not provide motivation to modify the teachings therein to arrive at such a method. Raz teaches administration of an ISS prior to exposure to an antigen. Raz does not suggest that it would be beneficial or advantageous to modify this method by administering the ISS after the exposure to antigen has occurred, and thus provides no motivation for the claimed methods.

Schwartz does not teach use of an ISS to treat or delay development of a papillomavirus infection by administration at the site of exposure or at the site of a lesion in the absence of papillomavirus antigen as claimed, and provides no motivation to do so. Schwartz does not suggest

that it would be beneficial or advantageous to administer the ISS without co-administration of a papillomavirus-derived peptide, and thus provides no motivation for the claimed methods.

None of the cited references provides motivation to modify the methods taught therein to arrive at the claimed methods, as required to support a *prima facie* case of obviousness.

3. The cited references do not provide a reasonable expectation of success with respect to the claimed methods.

The third requirement for a *prima facie* showing of obviousness is that one of ordinary skill in the art must have had a reasonable expectation of success in practicing the claimed invention at the time of filing. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); MPEP §2143.02. In the present case, nothing in the cited references or the knowledge in the art at the time of filing would have provided a skilled artisan with a reasonable expectation of success in practicing the claimed invention, as required for a *prima facie* case for obviousness.

It is a threshold requirement that all limitations be present in the cited references before it is even relevant whether there was a reasonable expectation of success by one of ordinary skill in the art. In the present case, as discussed above, the cited references do not disclose all of the elements of the claimed invention, either singly or in combination. Therefore, there could have been no reasonable expectation of success, since one of skill in the art could not have discerned each and every limitation of the claimed invention in the cited references.

As discussed above, the teachings of Bauman do not provide a reasonable expectation of success because Bauman teaches administration of IFN-α via a different route of administration. A skilled artisan would not expect success switching from systemic administration of IFN-α, as taught by Bauman, to local administration of an ISS-containing polynucleotide, as presently claimed. Further, Bauman teaches *direct* administration of IFN-α, versus administration of an ISS, which allegedly induces IFN-α production *indirectly*. Since none of the cited references teaches an amount of IFN-α induced *in vivo* per unit dose of ISS, it would not be possible for one of skill in the art to extrapolate from the teachings of Bauman to determine an appropriate dosage of an ISS to

achieve the therapeutic effect on HPV taught by Bauman, and hence there would be no reasonable expectation of success in practicing the claimed methods.

As discussed above, Beutner teaches use of imiquimod, a compound structurally unrelated to the claimed polynucleotides, and also teaches that it is unknown which cytokine is responsible for the clinical response of HPV to this compound. A person of skill in the art would not have a reasonable expectation of success in substituting an ISS for imiquimod in view of the structural dissimilarity of the compounds and in view of the lack of disclosure as to the mechanism of action of imiquimod.

Yamamoto does not teach or suggest treatment of any viral infection. Yamamoto discusses use of oligonucleotides with palindromic structures for treatment of tumors. Disclosure of antitumor activity would not provide a reasonable expectation of success for treatment of a viral infection.

As discussed above, neither Raz nor Schwartz teach administration of an ISS in the absence of papillomavirus antigen at the site of exposure or the site of a lesion. Raz teaches administration of an ISS *before* exposure to antigen, and would not provide a reasonable expectation of success for treatment of papillomavirus *after* the individual has been exposed to the virus or has an active viral infection as claimed. Schwartz teaches administration of an ISS *in conjunction* with a co-administered papillomavirus peptide antigen, and would not provide a reasonable expectation of success for treatment of papillomavirus by administering an ISS-containing polynucleotide in the *absence* of papillomavirus antigen as claimed.

None of the references cited by the Examiner would have provided a person of skill in the art with a reasonable expectation of success with respect to the claimed methods at the time of filing.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

Double Patenting

Claims 9-12, 14, 25, and 27 are provisionally rejected as allegedly unpatentable on the basis of nonstatutory obviousness-type double patenting over claims 1-6 and 11 of copending Application No. 10/898,512. As the Examiner notes in the Office Action, this is a provisional rejection because the allegedly conflicting claims have not in fact been patented. Office Action, page 7, lines 17-18.[1] Applicants would like to defer addressing this issue because Application No. 10/898,512 has not yet issued as a U.S. patent.

[1] The Examiner states on page 7, lines 20-21, of the Office Action that "[t]he . . . rejection is, in part based on the specification of a previously issued patent, rather than the claims." This statement is incorrect, because Application No. 10/898,512 is not a "previously issued patent," as noted by the Examiner on page 7, lines 17-18.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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